

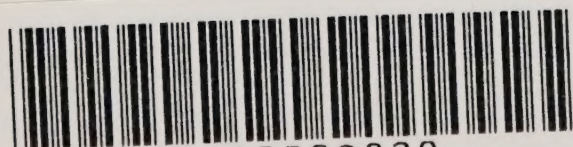
LIVER EXTRACT B.D.H.

For the Treatment of
Pernicious Anæmia and Allied Conditions



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LIVER EXTRACT

B.D.H.

For the Treatment of
Pernicious Anæmia and Allied Conditions

THE etiology of pernicious anæmia is still somewhat obscure, but the root cause is believed by some workers to be attributable to the absence of some principle, normally present in the liver, without which the bone-marrow cannot produce its normal quota of red cells. Muller ⁽¹⁾ takes the view that pernicious anæmia is due to over-action of the reticulo-endothelial system which results in the production of megalocytes at the expense of normal red cells; on the other hand, in normal conditions, the liver acts by inhibiting the megalocytic hyperplasia, thus giving an opportunity for the formation of normal red cells.

Causation factor

Minot holds the opinion that the primary defect is in the failure of the red cells to attain maturity, and that liver acts by stimulating the cells to complete their growth-cycle. His view gains much support from embryology, and bids fair to be generally accepted. But, even so, the nature of the force causing this abnormality in the growth of the red cells remains obscure.

On the other hand, McGowan ⁽²⁾ favours the view that under ordinary conditions of life the liver supplies a specific substance which controls and regulates the action of the bone-marrow, and that pernicious anæmia results not so much from an actual deficiency of this substance in the patient's liver as from an organic derangement of the marrow which causes a tendency towards a reversion to an amitotic basis; such a condition requires for its control a sufficiency of the specific active principle of the liver. In other words, the onus of originating the disease rests with the marrow—not with the liver.

Observations by a group of workers (Castle, Townsend and Heath ⁽³⁾) appear to confirm an etiological relationship between gastric achylia and pernicious anæmia, the former being a deficiency disease due to a defect in the protein-splitting function dependent on the achylia. This would suggest that deficiency of the specific substance in pernicious anæmia is due to a fault in digestion. Their work suggests, further, that the gastric defect may play an important rôle. In this connection the absence of hydrochloric acid in the gastric content in pernicious anæmia and the evidence of intestinal infection as shown by the high bacterial content of the fæces should be noted.

More recently it has been demonstrated by Morris, Schiff, Burger and Sherman ⁽⁴⁾ that there is present in normal gastric juice a substance—provisionally termed “Addisin”—which, when given intramuscularly to pernicious anæmia patients, produces a marked reticulocyte response. It is suggested that this active substance may be of the nature of an internal secretion or hormone.

It seems possible that such a hormone may be secreted by the stomach of the normal individual, and that a deficiency of this factor may be the cause of pernicious anæmia.

This gastrogenous theory is in accord with the results of the researches of Castle which show that the gastric juice in pernicious anæmia is actually lacking in some unknown “intrinsic” factor the presence of which is essential for normal hæmatopoiesis.

Whatever may be the ultimate solution of the problem of the etiology of pernicious anæmia, it is clear from clinical experience that the administration of a potent extract of liver provides a highly-effective means of treating the disease.

Characteristics of pernicious anæmia

The onset of pernicious anæmia is insidious, the patient gradually becoming conscious of failing strength and increasing breathlessness on exertion. The complexion becomes waxy and of a faint lemon-yellow tinge; there may be small petechial hæmorrhages under the skin. The general nutrition may not appear to be much affected, this symptom,

combined with the striking pallor, being characteristic. Digestive disturbances, also diarrhoea, are often present. In the later stages evidences of lateral and posterior degeneration of the cord may be present.

The blood picture in an ordinary case is characteristic, the red cells being as low as 1,000,000 per c.mm. with nucleated cells and megalocytes predominating. Leucopœnia is present, and the colour index is high.

As already stated, the actual cause of the disease is not yet known for certain; for the present it can only be said that pernicious anæmia is probably a deficiency disease in which the patient is lacking in some unknown factor which is specific for normal blood production. The fact remains, however, that such deficiency can be counteracted by the ingestion of a certain active principle which is present in liver.

Need of
extra ingestion
of active
principle of
liver

LIVER THERAPY IN PERNICIOUS ANÆMIA

The use of liver therapy in pernicious anæmia is the outcome of experimental work by Whipple and Robscheit-Robbins ⁽⁵⁾ who established the fact that a diet rich in liver had a beneficial effect in the hæmorrhagic anæmia of dogs. Further work (Minot and Murphy) ⁽⁶⁾ ⁽⁷⁾ along similar lines, but with human subjects, led to what may be described as one of the epoch-making discoveries in modern medicine, namely the spectacular curative effect of raw liver administration. Experience in clinical practice confirms the earliest findings, and liver therapy has become the routine treatment for pernicious anæmia.

History

Since the use of liver in the treatment of pernicious anæmia has become general, many attempts have been made to isolate the responsible therapeutic principle. In a résumé of a report by West and Howe ⁽⁸⁾ it is noted that these two workers describe the isolation of an active crystalline substance. Dakin, West and Howe (Columbia Univ., New York) show that this substance is a compound of β -hydroxyglutamic acid and γ -hydroxyproline,

Discussion on
therapeutic
principle of
liver

both of which are protein degradation products. In the same résumé the opinion is expressed that "*the action of liver depends on two factors, the inorganic salt contents and a complex polypeptide, which act as inducers or as inhibitors of megaloblast formation*".

In a later report, West and Howe ⁽⁹⁾ claim to have isolated from liver a tribasic acid—a pyrrole derivative—which they state is active in stimulating reticulocyte production.

Further, in regard to the mechanism of liver diet in pernicious anæmia, one worker affirms ⁽¹⁰⁾ ⁽¹¹⁾ that in this disease there is an absence of methæmoglobin in the blood; when liver therapy is instituted, however, methæmoglobin reappears and regenerative processes set in. From this it is assumed that the active substance in the liver is a producer of methæmoglobin, in that it causes a disintegration of the immature erythrocytes associated with the disease by changing the hæmoglobin into methæmoglobin.

The result is that the bone marrow is stimulated "*to such an extent that it changes its action and again produces erythrocytes that have a greater resistance*".

The erythrocytes in their turn disintegrate quickly, and, if sufficient liver be given, equilibrium is established between formation and disintegration. It is to be noted that the greater the purity and the concentration of the liver preparation employed, the more rapid the change of hæmoglobin into methæmoglobin.

LIVER THERAPY IN OTHER ANÆMIAS

Liver therapy was confined at first to sufferers from true pernicious anæmia, but considerable evidence is available of its value in cases of anæmias other than the true pernicious type ⁽¹²⁾, particularly in those cases which resemble the pernicious form in that they appear to be associated with megaloblastic hyperplasia of the bone-marrow, such as the anæmias of pregnancy and sprue.

In anæmias
of pregnancy
and sprue

In considering the nature and treatment of sprue it has been stated ⁽¹³⁾ that "*the etiology of sprue is not known, but it is probably an infective condition; it has a definite incubation period, and is subject to periods of latency and recrudescence. It appears as a specific inflammation ranging throughout the intestinal tract, associated with aphthous states of the mouth and tongue, and destruction of the intestinal mucosa; it results in diminished power of absorption, with consequent starvation, loss of weight, and severe anæmia. . . . The treatment is chiefly dietetic, aiming at the restoration of the power of absorption; it is especially necessary to re-establish a healthy blood picture*".

Etiology of sprue

Two workers ⁽¹⁴⁾ report, inter alia, gratifying results in ten cases of sprue, the response to liver treatment being better and quicker even than is the case with pernicious anæmia. It is recommended that a full, balanced diet with a sufficiency of vitamins be maintained throughout the period of the treatment.

IMPRACTICABILITY OF LIVER DIET

Notwithstanding the success achieved experimentally by raw liver treatment, it was found to possess certain drawbacks, not the least of which was the fact that many patients could not tolerate the daily ration of half a pound of liver—the smallest quantity recommended to produce optimum results. On the other hand, in any endeavour to make the liver more palatable by cooking it, there is always the risk that the therapeutic activity of the liver may be destroyed in the cooking.

In cases of anæmia of pregnancy there is also another aspect of the problem of the ingestion of fresh raw liver apart from the question of unpalatability. It has been found ⁽¹⁵⁾ that there is possible danger in high liver feeding during pregnancy when there is a tendency towards nephritis or toxæmia; careful observations should be made of the urine and blood pressure in all such cases. On the other hand, there is evidence that this danger does not exist if the liver be taken in the form of an extract.

INTRODUCTION OF LIVER EXTRACT B.D.H.

In view of the foregoing, the highly-active powdered Liver Extract B.D.H., which contains in small bulk the therapeutic principles of the original fresh liver, has overcome many of the difficulties associated with the administration of liver in anæmia. Liver Extract B.D.H. is manufactured by a process ⁽¹⁶⁾ tested and found efficient by the Medical Research Council, and it can be relied upon always for stability and constancy in activity.

CLINICAL TRIALS

In pernicious anæmia

Reports have been published on the clinical trials made in various hospitals upon samples of liver extract distributed by the Medical Research Council ⁽¹⁷⁾. In these trials the curative value of the extract was gauged by the rate of increase of the young red cells (reticulocytes). In practice it was found that, simultaneously with this increase, there was a distinct feeling of general improvement in the patient, and this was followed by a progressive increase in the count of red blood corpuscles.

Of the thirty-four cases treated, thirty-two responded to the treatment, but nine of these were ruled out owing to complications such as a possibility of natural remissions and the influence of some previous treatment.

In twenty-three cases the improvement could be attributed with certainty to one cause only—the administration of the liver extract.

The daily dose given was the equivalent of half a pound of fresh liver, the dose recommended by Minot and Murphy ⁽¹⁸⁾.

The rise in the percentage of reticulocytes reached a maximum in 12 to 15 days, whilst the count of the red blood corpuscles rose from 750,000 per c.mm. at the beginning of the treatment to 5,000,000 after 34 days' treatment.

Larger doses induced a quicker response, but the "half-pound" daily dose is recommended as the most satisfactory. The effects produced by the extract are described as "*identical with those obtained with liver itself*".

In addition to the work carried out by the Medical Research Council, clinical experiments have been made in this country, with whole liver and with liver extract, by Fraser and others. These workers reported their results ⁽¹⁹⁾, summarising them as follows:—

"Nineteen patients with pernicious anæmia have been treated with whole liver or a liver extract. Nine of them were in the first attack or in a relapse, and seven of these showed a prompt response to treatment, with a temporary rise in the percentage of reticulated red cells in the circulating blood, and a steady increase in the total red cells and the hæmoglobin. The reason for the failure in the treatment in the other two patients is not clear.

Ten patients commenced treatment during the remission stage or received other forms of treatment in addition, so that observations on the immediate effects of the treatment were not possible. The condition of these patients at the end of varying periods of treatment (up to six months) affords confirmatory evidence of the value of this treatment."

In addition to the striking benefit following the use of liver extract in the primary condition, Richardson ⁽²⁰⁾ believes that the secondary nervous symptoms not infrequently clear up, or materially improve, provided adequate treatment be maintained. In his opinion it is necessary to keep the red blood cell-count above 4 to 5 million per c.mm. in order to prevent involvement of the central nervous system.

In anæmia of pregnancy

In the treatment of the anæmia of pregnancy a typical case report shows an increase of 2,030,000 per c.mm. in the red cell-count as a result of the administration of Liver Extract B.D.H. for 23 days.

In sprue

Again, in a case of anæmia following sprue in which Liver Extract B.D.H. was administered for 36 days, an increase of 2,210,000 per c.mm. red blood corpuscles resulted.

Clinical evidence furnished by Minot and Murphy ⁽²¹⁾ in their later experiments, in conjunction with Cohn and others, with a non-protein liver extract prepared by the method of Cohn, also confirms the evidence produced in this country that liver extract, when properly prepared, is just as efficacious as whole liver.

ADMINISTRATION AND DOSAGE

The advantages of Liver Extract B.D.H. over whole liver—raw or cooked—lie in its simplicity in use and in its palatability.

Liver Extract B.D.H. is mixed with hot water in a manner exactly similar to that adopted with an ordinary meat extract. The contents of one tube—containing the active principles of half a pound of fresh raw liver—are emptied into a cup or other suitable vessel; the cup is then filled with hot water, the mixture being stirred during the process of dilution. Condiments may be added to suit the individual palate, and the mixture taken as an ordinary soup or beef tea. In this way it is quite palatable.

Liver Extract B.D.H. may be taken also in the form of a sandwich, or as a savoury sprinkled on toast, biscuit, or potato.

In pointing out the advantages resulting from the palatability of the extract and its simplicity in use, Cohn and others emphasise the necessity of prescribing an adequate and well-balanced diet throughout the course of the treatment.

The opinion is expressed by Minot and confirmed by other workers ⁽²²⁾ that “*the response to this treatment depends upon the total amount of liver principle given during a certain period of time rather than on the amount taken each day. A single large dose (. . . equivalent to 5 lb. of liver) produces a reticulocyte response lasting for about ten days and equal in intensity to that obtained from a daily dose . . . (half a pound of liver) given for ten days. The active principle of liver appears to be utilized quantitatively, the effect lasting for a given time*”.

As far as is known at present, there are no conditions in which Liver Extract B.D.H. is contra-indicated, but a full diet is an essential accompaniment to the treatment.

The maintenance dose varies ; hence, in order to estimate correctly the amount of liver required for the individual case, progress should be observed by blood counts at monthly intervals. If the treatment be carried out faithfully, in all probability the patient will remain well ; on the other hand, there is grave danger of relapse if it be discontinued.

According to Vaughan ⁽²³⁾, sepsis, nervous lesions and arteriosclerosis are factors which may hinder the absorption of liver. In consequence, when these conditions accompany pernicious anæmia, the average dose should be doubled or even trebled. Old people also frequently require an abnormally-large quantity of liver extract in order to obtain an appropriate response.

In all such cases it is important that an “adequate” dose be prescribed, and it is observed that it often happens that a dose is only really “adequate” when it may appear to be “absurdly large”.

Knott ⁽²⁴⁾ has emphasised the necessity, in order to prevent relapses, of treating the alimentary sepsis directly in addition to administering the liver extract.

MODE OF ISSUE

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